LETTER TO THE EDITOR

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Comments on "Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus"

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We read with great interest the recent article "Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus" by Khan and colleagues.[1]

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially severe adverse side effect of antiresorptive agents, and although a significant body of literature has been produced, there remains little evidence-based guidance for clinicians with respect to most aspects of this disease. Therefore, we applaud the attempt of Khan and colleagues to provide a much-needed systematic review.

However, it is important that any review on this topic is addressed on the basis of the best available evidence and a balanced analysis of the literature. More importantly, systematic reviews require rigorous research methods and a clear and transparent presentation of results in order to limit bias and maximize readability.[2–4] In the work of Khan and colleagues,[1] we have identified several issues that we suggest carry a risk of affecting the validity of their results.

Assessing the risk of bias is a crucial part of systematic reviews.[5,6] Khan and colleagues presented the criteria they used to assign level of evidence and grade recommendations, but unfortunately provided little information regarding qualitative assessment of reviewed studies, related risk of bias, as well as the process of article selection. Overall, it is hard to understand how and why articles were selected or excluded.

The presentation of data on incidence and prevalence makes the interpretation of the results difficult. It is well established that incidence data without definition of a time period can be meaningless;[7] nevertheless, results upon incidence of MRONJ are in several instances presented without mentioning the relevant time frame. There are also inconsistencies between different sections of the article: For example, in the abstract, it is stated that "in the osteoporosis patient population MRONJ incidence is estimated at 0.001 to 0.01%," whereas different figures are reported in the results (0.15% to <0.001% person-years of exposure). Furthermore, the authors state that the prevalence of MRONJ in the oncological setting ranges from "0 to 0.186%" whereas the work of Walter and colleagues, which they cite, reports a prevalence of 18.6%.[8]

Khan and colleagues report that the incidence of MRONJ in the osteoporosis population would only be "marginally higher than the incidence in the general population," which in the abstract is reported to be <0.001%.[1] This statement is quite

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confusing because it remains unclear what they mean by "incidence of jaw necrosis in the general population." Possibly the authors refer to other disorders that may cause jaw necrosis in the absence of antiresorptive therapy. We wonder whether it is appropriate to associate different populations with different disorders when incidence/prevalence is discussed in a systematic review. Also, we could not find any clear reference in the text supporting the reported $<0.001\%$ incidence; it remains uncertain where this figure comes from.

We also found it singular and rather unusual for a systematic review to provide a detailed description of an unrelated, poorly characterized, and not widely accepted disease entity, namely oral ulceration and bone sequestration (OUBS).[1] Its relevance to the intended systematic review on MRONJ remains unclear. The articles cited in the main part of the paper (Introduction)[9–11] do not provide convincing evidence regarding the impact this questionable disease may have upon patients, and certainly they cannot suggest that a significant portion of cases of MRONJ could, in fact, represent misdiagnosed OUBS.

The definition of MRONJ continues to cause significant controversy. Khan and colleagues seem to disregard the suggestions of different independent research groups who have called for a change in the traditional definition[12] so as to include the nonexposed variant of MRONJ,[13–23] which can represent up to 25% of all cases.[13] We wonder whether the authors concluded that these articles were in some way flawed and, therefore, had to be excluded from the systematic review. It is also rather surprising that they decided not to embrace the revised 2014 AAOMS consensus, which agrees that individuals presenting with bone that can be probed via sinus tracts do fit MRONJ definition.[24]

With respect to MRONJ treatment, readers would expect a systematic review to provide a balanced and fair comparison of the outcomes of different interventions, both surgical and nonsurgical. However, Khan and colleagues suggest that "conservative therapy is the mainstay of care" with no robust convincing evidence in support of this statement. Although we agree that there is a lack of consensus, as well as very little information on the outcomes of denosumab-related ONJ, we think that this review does not provide a fair and comprehensive summary of current knowledge and available evidence.

For example, when mucosal healing is considered the primary outcome,[25–28] a number of articles have reported that less than one-third of patients managed with long-term conservative treatment, especially in the oncological setting, would show evidence of mucosal healing (23% and 14.9% of Hoff and colleagues[29] and Nicolatou-Galitis and colleagues[30] case series, respectively). This means that the majority of MRONJ patients managed conservatively would present persistent jawbone exposure, which not only can affect their quality of life[31] but may also limit the oncological treatment options, including further antiresorptive treatment.[32,33] Although conservative treatment might be adequate to slow down disease progression and control pain and infections, there is increasing evidence supporting surgical treatment protocols. Case series from different research groups report percentages of mucosal healing that are consistently around and above 80%, with outcome endpoints ranging from 3 months to 7 years post-treatment. Examples include Carlson and colleagues (92%), [26] Stockmann and colleagues (89%), [34] Bedogni and colleagues (90%), [35] Schubert and colleagues (89%), [36] and Jacobsen and colleagues (78%). [37] Comparative studies also seem to confirm these results.[38,39] Finally, both the systematic review by Rupel and colleagues[40] and another recent systematic review meeting PRISMA guidelines[6] suggest that surgical therapy can be superior to conservative management.[41]

We feel that these are important aspects completing the review of Khan and colleagues.[1]

References

1. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015;30(1):3–23.
2. Sharif MO, Janjua-Sharif FN, Ali H, Ahmed F. Systematic reviews explained: AMSTAR-how to tell the good from the bad and the ugly. Oral Health Dent Manag. 2013;12(1):9–16.
3. Yuan Y, Hunt RH. Systematic reviews: the good, the bad, and the ugly. Am J Gastroenterol. 2009;104(5):1086–92.
4. Holmdahl L. A misleading meta-analysis of seprafilm. World J Surg. 2008;32(8):1888–9; author reply 1890–1.
5. Humphrey PR. Systematic reviews of diagnostic test evaluations: what's behind the scenes? ACP J Club. 2004;141(3):A14.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
7. Noordzij M, Dekker FW, Zoccali C, Jager KJ. Measures of disease frequency: prevalence and incidence. Nephron Clin Pract. 2010;115 (1):17–20.
8. Walter C, Al-Nawas B, Grotz KA, et al. Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. Eur Urol. 2008;54(5):1066–72.
9. Peters E, Lovas GL, Wysocki GP. Lingual mandibular sequestration and ulceration. Oral Surg Oral Med Oral Pathol. 1993;75(6): 739–43.
10. Scully C. Oral ulceration: a new and unusual complication. Br Dent J. 2002;192(3):139–40.
11. Sonnier KE, Horning GM. Spontaneous bony exposure: a report of 4 cases of idiopathic exposure and sequestration of alveolar bone. J Periodontol. 1997;68(8):758–62.
12. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2007;65(3):369–76.
13. Fedele S, Bedogni G, Scoletta M, et al. Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed. Br J Oral Maxillofac Surg. 2015;53(1): 13–7.
14. Fedele S, Porter SR, D'Aiuto F, et al. Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. Am J Med. 2010;123(11):1060–4.
15. Hutchinson M, O'Ryan F, Chavez V, et al. Radiographic findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure. J Oral Maxillofac Surg. 2010;68(9): 2232–40.
16. Junquera L, Gallego L. Nonexposed bisphosphonate-related osteonecrosis of the jaws: another clinical variant? J Oral Maxillofac Surg. 2008;66(7):1516–7.
17. Mawardi H, Treister N, Richardson P, et al. Sinus tracts—an early sign of bisphosphonate-associated osteonecrosis of the jaws? J Oral Maxillofac Surg. 2009;67(3):593–601.
18. Patel S, Choyee S, Uyanne J, et al. Non-exposed bisphosphonate-related osteonecrosis of the jaw: a critical assessment of current definition, staging, and treatment guidelines. Oral Dis. 2012;18(7): 625–32.
19. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg. 2009;67(5 Suppl):2–12.

20. Yarom N, Fedele S, Lazarovici TS, Elad S. Is exposure of the jawbone mandatory for establishing the diagnosis of bisphosphonate-related osteonecrosis of the jaw? J Oral Maxillofac Surg. 2010;68(3):705.
21. Schiodt M, Reibel J, Oturai P, Kofod T. Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(2):204–13.
22. Colella G, Campisi G, Fusco V. American Association of Oral and Maxillofacial Surgeons position paper: bisphosphonate-related osteonecrosis of the jaws—2009 update: the need to refine the BRONJ definition. J Oral Maxillofac Surg. 2009;67(12):2698–9.
23. Bedogni A, Fusco V, Agrillo A, Campisi G. Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). Oral Dis. 2012;18(6):621–3.
24. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72(10):1938–56.
25. Assaf AT, Zrnc TA, Riecke B, et al. Intraoperative efficiency of fluorescence imaging by Visually Enhanced Lesion Scope (VELscope) in patients with bisphosphonate related osteonecrosis of the jaw (BRONJ). J Craniomaxillofac Surg. 2014;42(5):e157–64.
26. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2009;67(5 Suppl):85–95.
27. Pautke C, Bauer F, Otto S, et al. Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: first clinical results of a prospective pilot study. J Oral Maxillofac Surg. 2011; 69(1):84–91.
28. Vescovi P, Manfredi M, Merigo E, Meleti M. Early surgical approach preferable to medical therapy for bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2008;66(4):831–2.
29. Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res. 2008;23(6): 826–36.
30. Nicolatou-Galitis O, Papadopoulou E, Sarri T, et al. Osteonecrosis of the jaw in oncology patients treated with bisphosphonates: prospective experience of a dental oncology referral center. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(2):195–202.
31. Kyrgidis A, Triaridis S, Kontos K, et al. Quality of life in breast cancer patients with bisphosphonate-related osteonecrosis of the jaws and patients with head and neck cancer: a comparative study using the EORTC QLQ-C30 and QLQ-HN35 questionnaires. Anticancer Res. 2012;32(8):3527–34.
32. Then C, Horauf N, Otto S, et al. Incidence and risk factors of bisphosphonate-related osteonecrosis of the jaw in multiple myeloma patients having undergone autologous stem cell transplantation. Onkologie. 2012;35(11):658–64.
33. Otto S, Schreyer C, Hafner S, et al. Bisphosphonate-related osteonecrosis of the jaws—characteristics, risk factors, clinical features, localization and impact on oncological treatment. J Craniomaxillofac Surg. 2012;40(4):303–9.
34. Stockmann P, Vairaktaris E, Wehrhan F, et al. Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up. Support Care Cancer. 2010;18(4):449–60.
35. Bedogni A, Saia G, Bettini G, et al. Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. Oral Oncol. 2011;47(5):420–4.
36. Schubert M, Klatte I, Linek W, et al. The saxon bisphosphonate register—therapy and prevention of bisphosphonate-related osteonecrosis of the jaws. Oral Oncol. 2012;48(4):349–54.
37. Jacobsen C, Metzler P, Obwegeser JA, Zemann W, Graetz KW. Osteopathology of the jaw associated with bone resorption inhibitors: what have we learned in the last 8 years? Swiss Med Wkly. 2012;142:w13605.
38. Mucke T, Koschinski J, Deppe H, et al. Outcome of treatment and parameters influencing recurrence in patients with bisphosphonate-related osteonecrosis of the jaws. J Cancer Res Clin Oncol. 2011; 137(5):907–13.
39. Graziani F, Vescovi P, Campisi G, et al. Resective surgical approach shows a high performance in the management of advanced cases of bisphosphonate-related osteonecrosis of the jaws: a retrospective survey of 347 cases. J Oral Maxillofac Surg. 2012;70(11):2501–7.
40. Rupel K, Ottaviani G, Gobbo M, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol. 2014;50(11):1049–57.
41. Fliefel R, Tröltzsch M, Kühnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int J Oral Maxillofac Surg. Epub 2015 Feb 25.